REMARKS

Claims 1-11 and 13-17 are pending in the application. Claims 12 and 18-39 are withdrawn as a result of the restriction requirement.

The Examiner has not offered any explanation for the withdrawal of claims 12 and 35, which were part of Group I in the Restriction Requirement mailed July 5, 2007. Applicants' written and telephonic election of the restriction sites does not affect the status of these claims as part of group I. Accordingly, Applicants request that these claims be reinstated.

The claims and the specification have been amended to insert sequence identifiers, to remove hyperlinks, to correct typographical errors and to correct formalities.

No new matter has been added.

Sequence Listing Statement

Applicants submit the sequence listing in accordance with 37 C.F.R § 1.821(a) – (d) and 37 C.F.R § 1.822-1.825, and which is generated from originally filed specification and figures. The undersigned representative hereby declares that in accordance with 37 C.F.R § 1.821(g) the content of the sequence listing does not constitute new matter. Under EFS-Web filing procedures, Applicants believe that they need to submit only an electronic version of the sequence listing in order to comply with the rules for submission of sequence listing.

Objections to the Drawings

Figure 2 is objected to because of missing amino acid sequence identifiers. However, the four amino acid characters shown in Figure 2 are abbreviations for the names of chromogenic substrate constructs used in the experiments. (*See* Specification, Description of the Figures, p. 17). The full names are as follows: "Ac-IEPD-pNA, Ac-LEED-pNA, Ac-VEID-pNA, Ac-YVAD-pNA, Ac-DEVD-pNA . . . Ac-IEPD-pNA." *Id.*

Because Figure 2 merely provides abbreviated names and not sequences *per se,* SEQ ID NO. identifiers are not required in FIG 2.

Applicants respectfully request the Examiner to withdraw this objection.

Objections to the Specification

A. Objection to missing SEQ ID NOs: and presence of URLs in Specification.

The specification stands objected to as allegedly containing deficient sequence identifiers. Applicants have provided additional SED ID NOs. in the attached substitute specification where the specification provides at least a minimum of four peptides.

In some instances, the single letter abbreviations for four peptides are used in the names of the constructs. For example "pro-IEGR-GrB-H6" is the name of a construct, not a disclosure of a four amino acid peptide. The four amino acids do not constitute a disclosure of an isolated amino acid sequence. The disclosed constructs are significantly longer than four amino acids and their respective sequences are provided in the existing sequence listing. (*See* Specification, p. 15, second paragraph and SEQ ID NOs 1-8). Thus, no SEQ ID NO: identifiers have been assigned to construct names. Also described in the specification are vector constructs with a four amino acid reference in their name (*e.g.,* T7-IEPD-Grb-H6). No sequence identifiers have been assigned to vector construct names.

In addition, the Applicant has reviewed the specification for URLs and other hyperlinks. These have been removed as requested by the Examiner.

No new matter has been introduced to the application based for the above-mentioned amendments to the specification. Applicants respectfully request the Examiner to withdraw this objection.

B. Objection to Disclosure for Alleged Conflicting Sequence Structure

The Examiner objected to the specification for the disclosure of conflicting information regarding the sequence of GrB-H6 and the structure of pro-IEGR-GrB-H6 (SEQ ID NO: 1). Applicants have reviewed the sequences for both constructs. Sequences are accurate and consistent with the originally disclosed sequence listing disclosure as explained herein.

For pro-IEGR-GrB-H6 (SEQ ID NO:1), the first seven amino acids correspond to the Fxa recognition sequence, MGSIEGR (*see* top of page 32). Amino acid 8 for SEQ ID NO. 1 corresponds to Ile21 in Granzyme B (Ile 16 in chymotrypsin numbering) (*see* Specification, top of page 32). SEQ ID NO. 1 correctly identifies the position of Tyr247.

The three amino acids prior to the His tag are a part of the disclosed T7 cloning vector in which the His tag was cloned. Specifically, they correspond to restriction sites, including EcoR1 site. (*see* page 33, second paragraph). Page 13 of the specification explains that one of skill in the art would recognize Granzyme B protease variants where one or more amino acid residues are added, or deleted or conservative variations. Thus, with regard to the above discrepancies, the sequences are not conflicting and are fully supported by the disclosure.

The applicants have amended the specification at the beginning of Example 1, on the top of page 32, to reflect that the Granzyme B sequence terminates with Tyr247. This correction adds no new matter as the Granzyme B sequence ending with Tyr247 was disclosed and fully supported throughout the original sequence listing (SEQ ID NO: 1, as one example).

In light of the amendment and discussion above, Applicants respectfully request the withdrawal of objections to conflicting sequence disclosure.

Objections to the Claims

A. The Examiner objected to the claims for not beginning with a sentence.

The claim set has been amended to recite "We claim:" prior to claim 1.

B. The Examiner objected to claims 1-11 and 13-17 for reciting non-elected subject matter.

Applicants are unclear about the basis and meaning of this rejection.

Applicants respectfully remind the Examiner that Invention I, which corresponds to claims 1-17 and 35, was acknowledged by the Examiner as the Applicant's election in the first paragraph of the current Office Action (January 16, 2008). Claims 1-11 and 13-17 were at the time of election drawn to and continue to be drawn to a method for cleaving a fusion protein using a Granzyme B polypeptide. Therefore, Applicants respectfully request the Examiner to withdraw this objection.

C. The Examiner objects to claims 2-5 for disclosing sequences not indentified by a sequence identifier.

Sequence identifiers for claims 2-5 have been provided in the amended claims attached herewith. Applicants respectfully request the Examiner to withdraw this objection.

Rejections under 35 USC §112, second paragraph

Claims 1-11 and 13-17 stand rejected under 35 USC 112, second paragraph, for alleged indefiniteness for failing to particularly point out and distinctly claim the subject matter for which applicants regard as the invention.

A. Claim 5 (failing to define P1', P2', and P3')

Claim 5 stands rejected as indefinite for allegedly failing to define the terms P1', P2', and P3'. Applicants respectfully disagree with the rejection.

The Specification defines P1', P2' and P3' with adequate particularity. For example, the specification provides "Granzyme B would recognize and cleave off polypeptides from a fusion protein after the P1 position without any strict requirements for specific amino acid residues at the P1'-P4' positions, i.e. the amino acid positions following the cleavage site." (*see* pp. 8-9). Accordingly, as the Examiner recognizes, P1', P2' and P3' can be any amino acid.

B. Claim 17 (failing to limit the claim)

Claim 17 was amended to depend from claim 16, and thus is in proper format.

C. Improper antecedent basis for claims 2-11, and 13-17

Claims 2-11, and 13-17 were amended to reflect proper antecedent basis and suggested by Examiner.

D. Improper antecedent basis for claim 1(c)

Claim 1 was amended to reflect proper antecedent basis as suggested by Examiner.

Rejections under 35 USC §112, first paragraph, enablement

Claims 1-11 and 13-17 stand rejected under 35 USC 112, first paragraph, for alleged lack of enablement. According to the Examiner, the specification does not reasonably provide enablement for a method to cleave a fusion protein comprising any Granzyme B motif using any Granzyme B enzyme having any structure. Applicants respectfully disagree with the rejection because the specification provides sufficient guidance to enable one of skill to make and use the invention in a manner reasonably correlated with the scope of the claims.

The invention does not encompass "any protein having any structure to cleave a fusion protein" as asserted by the Examiner (*see* Office Action, p. 8). Instead, Granzyme B is the specific protease and Granzyme B is distinct from other proteases known in the art, such as Xa. "Granzymes are granule-stored serine proteases that are implicated in T cell and natural killer cell-mediated cytotoxic defense reactions after target cell recognition. . . Granzyme B is one type of granzymes, and upon target cell contact it is directionally exocytosed and enters target cells . . ." (*See Specification,* p. 7). "Human Granzyme B protease occurs in most human tissues where its biological function is well known." (*Id.* p. 8).

As for the species variations, the specification adequately describes human Granzyme B sequences, whereas the specification provides other Granzyme B species, including mouse and rat. (*See* p. 12, last paragraph and claim 11). Granzyme B nucleotide and amino acid sequence for both mouse and rat were published prior to the filing date, Accession No: CT010272 (July 21, 2005) and Accession No: M34097 (April 27, 1993), respectively. It would not constitute undue experimentation for one of skill in the art to utilize known Granzyme B sequence species variants to produce the claimed invention.

Morever, dozens of Granzyme B sequence variants were disclosed in the pending application, not two as alleged by the Office Action. Over twenty cleavage sites were specifically disclosed in the specification (p. 10) and in the original claim 3 and 20. The Sequence Listing alone (SEQ ID NOs: 1-8) provides 8 Granzyme B variants with modified upstream amino acids (amino acids 4-7) and/or modified downstream amino acid 228 (C to A; C to T; C to V; C to F). The Examples provide a plethora of Granzyme B variants and their activities. (*see* pages 32-33, 39-40). The disclosed Granzyme B protease variants are capable of cleaving fusion proteins as described in the Experimental Examples. (*See* pages 56 and 61, which teach the cleavage rates for multiple forms of Granzyme B).

As explained on page 13 of the specification, variations and substitutions of amino acids was well-known. This invention comprises discrete amino acid substitutions, not protein domain swapping. Such simple amino acid substitutions would not result in unpredictable protein structure or function. The substitution of individual amino acids was well known in the art and enabled by the teachings of the disclosure as well as the state of the art at the time of filing. Thus, the disclosure fully supports the scope of the claimed invention.

In addition to the outline of the disclosure cited above, Applicant's respond to points A-H cited by the Office Action. Specifically the Office Action alleged that the specification does not support the broad scope of Claims 1-11 and 13-17 because the specification does not establish: (A) the structure of any enzyme that can be used in the

recited method: (B) regions of the protein structure which may be modified without affecting the cleavage activity; (C) the general tolerance of the cleavage activity to modification and extend of such tolerance; (D) the structure of all motifs that can be cleaved by any Granzyme B; (E) regions of the motif structure which may be modified without affecting the ability to be cleaved; (F) the general tolerance of the cleavage motif to modification and extent of such tolerance; (G) a rational and predictable scheme for modifying any residues of a Granzyme B or cleavage motif with an expectation of obtaining desired biological function and (H) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

The filed disclosure (A) provides sufficient teaching of a specific Granzyme B protease and Granzyme B sequence variants experimentally exhibiting protease activity as described immediately above. (S*ee* pgs. 10, 32, 33, 39, 40, 56, and 61, SEQ ID NOS: 1-8). The claims do not encompass 'any enzyme' as alleged in the Office Action. The disclosure provides (B) specific amino acids that can be modified to *improve* cleavage activity. (*See* p. 61). The disclosure (C) outlines the impact of protein modifications and the tolerance of enzyme cleavage activity throughout Examples 3, 4, 6 & 8. The specification and claims provide (D) specific amino acid cleavage sites (over 20) (*see, e.g.,* p. 10) as well as the patterns of amino acid cleavage sites (*see* pp. 8-10), thus the claimed cleavage motifs are within scope of the disclosure. Again, (E) the above variants contain multiple amino acid substitutions and yet maintain cleavage activity (Example 8). (F) The plethora of cleavage motif modifications coupled with their continued activity provides sufficient teachings to enable one of skill in the art to predict cleavage motif variations and their tolerance for continued activity. Similar to E and F above, the (G) vast number of modified Granzyme variants would permit one of skill to modify the cleavage motif or residues with an expectation of obtaining the desired function (e.g. cleavage). (H): Based on the dozens of variants and the disclosure of experimental Examples (specific pages cites above), Applicants have provided sufficient guidance to enable one of skill in the art to practice a method for preparing fusion proteins via the cleavage of a Granzyme B site with a Granzyme B protease.

Accordingly, the scope of the claimed invention is enabled by the disclosure and one of skill in the art could practice the claimed invention without undue experimentation. Applicants respectfully request Examiner to withdraw this rejection.

Rejections under 35 USC §112, first paragraph, written description

Claims 1-11, and 13-17 stand rejected under 25 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that inventors had possession of the claimed invention at the time of filing. The Examiner explained that only two representative species are provided but that the claims are directed to a genus of molecules. Applicants respectfully disagree with the rejection.

As stated above, Granzyme B is a distinct protease from other proteases, such as Xa, and is well known in the art. Proteases beyond Granzyme B are not encompassed by the present invention. Dozens of Granzyme B variants were disclosed in the pending application. Over twenty cleavage sites were specifically disclosed in the specification (pg. 10) and in the original claim 3 and 20. The Sequence Listing (SEQ ID NOS: 1-8) provides eight Granzyme B variants with modified upstream amino acids (amino acids 4-7) and/or modified downstream amino acid 228 (C to A; C to T; C to V; C to F). The following pages in the Examples provide multiple Granzyme B variants and their activities: 32-33, 39-40). Therefore, the filed disclosure provided adequate representative species and sufficiently described the claimed invention such that one of skill in the art would recognize that Applicant's were in possession of Granzyme B enzyme and Granzyme B cleavage motifs.

Claims 4 and 5 are further rejected under 35 USC 112, first paragraph for failure to teach representative species of Granzyme B cleavage motifs, wherein residues P1', P2', P3', and P4' are part of the polypeptide. As discussed under Part 4 (B) above, the specification provided a description of the amino residues that constitute the P' residues. "Granzyme B would recognize and cleave off polypeptides from a fusion protein after the P1 position without any strict requirements for specific amino acid residues at the P1'-P4' positions, i.e. the amino acid positions following the cleavage site." (*See* pp. 8-9).

P1'-P3' can be any amino acid as assumed by the Examiner (*see* pg. 5 of the Office Action). Thus, the specification sufficiently described the claimed invention such that one of skill in the art would recognize that Applicants were in possession of Granzyme B cleave motifs including amino acid residues specific to P1', P2', P3', and P4' in the polypeptide of interest. Furthermore, 24 specific cleavage sites were provided in the specification (p. 10) and original claims 3 and 20.

Because one of skill in the art would believe the inventors were in possession of the claimed invention, Applicants respectfully request Examiner to withdraw this rejection.

Rejections under 35 USC §103

Claims 1-3, 6, 9-11 and 13-15

Claims 1-3, 6, 9-11, and 13-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al., 2000 in view of Harris et al., 1998 and further in view of Pharmacia, Inc. 1986. Applicants respectfully disagree with the rejection.

The combination of Johnson, Harris and Pharmacia, Inc. fails to render claims 1-3, 6, 9-11, and 13-15 obvious under 35 U.S.C. 103(a) for several reasons. First, Harris does not teach a four amino acid motif (IEAD) specific for the Granzyme B cleavage to prepare a protein in authentic form as stated in the Office Action. Instead, Figure 5 and the remainder of Harris discloses a six amino acid motif IEAD↓AL (P4 P3 P2 P1 ↓ P1' P2') that is essential for Granzyme B cleavage (see abstract and Figure 5). The disclosure of six amino acids, in particular the two after the cleavage (P1' P2'), teaches away from the cloning and preparation of an authentic protein of interest. The first two amino acids of the protein after the cleave site must include extraneous P1' P2' amino acids.

Furthermore, Harris does not teach or suggest the production of a polypeptide of interest in authentic form, but instead describes the cleavage of a variety of short synthetic amide substrates produced via a combinatorial library as shown in Tables 2 and 3. Harris merely identifies a handful of six amino acid sequences and the specific site of

Granzyme B cleavage. Harris provides no mention or suggestion to use Granzyme B for the purification of protein of interest in authentic form.

Johnson describes a fusion protein containing a Xa protease site. Xa is a distinct protease with its own subset of specific amino acids sequence requirements (cleavage motifs) and enzyme cleavage efficiencies. Johnson does not disclose the production of a protein of interest in authentic form. To the contrary, Johnson describes the characterization of protein, streptokinase Sk^U, domain fragments. (see pg 6441, ¶2).

The addition of Pharmacia to the combination of Harris and Johnson does not resolve the failure of the combination to teach or suggest the method of claim 1. Pharmacia is a one-page reference listing coupling gels for the immobilization of ligands via a specific functional group. The combination of Pharmacia's sepharose gel description coupled with Johnson's discussion of the distinctly different Xa protease, and Harris's six amino acid required Granzyme B cleavage site are insufficient to render the claimed invention, "a method for preparation of polypeptide of interest in authentic form by providing a fusion protein with Granzyme B protease", predictable or obvious to one of skill in the art.

Moreover, the claimed invention provides unexpected results. Compared to methods of preparing fusion proteins with other proteases known in the art, and in particular Xa protease, Granzyme B protease provides significant and unexpected improvement over the existing prior art. Granzyme B is (a) more specific than other proteases (does produce cleavages in the middle of the protein of interest) (*see* Specification, pp. 3-5, and 62); (b) permits the purification of authentic forms of proteins of interest (no extraneous amino acids at the amino terminus thereby improving native confirmation) (*id.*); and (c) provides a more efficient cleavage than other proteases (*id.*), which reduces production costs by reducing wasted uncleaved fusion protein (*id.,* pp. 3-4). In fact, Johnson describes a very inefficient cleavage efficiency of 50% with Xa (*see* paragraph cited in Office Action (p. 6441, ¶ 5 - p. 6442, ¶ 1)). Nothing in the prior art suggests to the skilled artisan the results that have been obtained with the claimed method.

Accordingly, claims 1-3, 6, 9-11, and 13-15 are patentable over the combination of Johnson, Harris and Pharmacia, Inc. because the combination of cited art fails to lead one of skill in the art to modify or combine the teachings to arrive at the claimed invention, or (2) because the results of the claimed invention were unexpected.

Claim 4

Claim 4 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al., 2000 in view of Harris et al., 1998 and further in view of Parenti et al., 1993.

Applicants respectfully submit that the combination of Johnson and Harris with Parenti does not resolve the failure of Johnson and Harris combination to teach or suggest the method of claim 1 or claim 2 as discussed above. Because claim 4 depends from claims 1 and 2, claim 4 includes all the elements of claim 1 and claim 2. Therefore, for the reasons discussed above regarding the patentability of claims 1 and 2, Applicants submit that claim 4 is patentable.

In addition, the combination of Johnson, Harris and Parenti does not render claim 4 obvious under 35 U.S.C. 103(a). Parenti merely describes a protein, G protein alpha, in which the second amino acid happens to be a glycine residue. Parenti does not teach an authentic protein form, or even a protein for used in the "generation of antibodies or biochemical assays" as cited by the Office Action. Thus, the reference fails to provide sufficient motivation to one of skill in the art to combine it with Johnson and Harris (described immediately above) to arrive at the invention of claim 4. Furthermore, sufficient secondary considerations exist due to the unexpected results associated with claimed method (*e.g.*, Granzyme B efficiencies and cleavage specificities, described immediately above).

Claim 5

Claim 5 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al., 2000 in view of Harris et al., 1998 and further in view of Martin et al. 2000.

Applicants respectfully submit that the combination of Johnson and Harris with Martin does not resolve the failure of the combination of Johnson and Harris to teach or suggest the method of claim 1 or claim 2 as discussed above. Because claim 5 depends from claims 1 and 2, claim 5 includes all the elements of claims 1 and 2. Therefore, for the reasons discussed above regarding the patentability of claims 1 and 2, Applicants submit that claim 5 is patentable.

In addition, the combination of Johnson, Harris and Martin does not render claim 5 obvious under 35 U.S.C. 103(a). Harris does not teach an eight amino acid sequence cleavage site (P4 P3 P2 P1 ↓ P1' P2' P3' P4'), but instead a 6 amino acid cleavage site (P4 P3 P2 P1 ↓ P1' P2') (see Abstract and Figure 5 as cited in Office Action). See also discussion of Harris and Johnson immediately above. Martin merely describes a protein, phospholipase C, in which the fourth amino acid happens to be a glutamate residue. Martin does not teach a method for preparation of a protein of interest in authentic form. Thus, the prior art references fail to teach the individual elements of the claimed invention, 'a method for preparation of polypeptide of interest in authentic form by providing a fusion protein with Granzyme B protease site comprising the general formula P4 P3 P2 P1 ↓ P1' P2' P3' P4'. Furthermore, the combination of the elements disclosed in Johnson, Harris and Martin would not motivate one of skill in the art to arrive at the claimed invention

Sufficient secondary considerations exist due to the unexpected results associated with claimed method (e.g. Granzyme B efficiencies and cleavage specificities, described under sub-part (A) above.

Claim 7

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boyer et al., 1992 in view of Harris et al., 1998.

Applicants respectfully submit that the combination of Boyer with Harris does not resolve the failure of Johnson, Harris, and Pharmacia to teach or suggest the method of claim 1. Because claim 7 depends from claim 1 (via claim 6), claim 7 includes all the elements of claim 1. Therefore, for the reasons discussed above regarding the patentability of claim 1, Applicants submit that claim 7 is patentable.

In addition, the combination of Boyer and Harris does not render claim 7 obvious under 35 U.S.C. 103(a). Harris does not teach a four amino acid motif IEAD as important for Granzyme B as cited in the Office Action, but instead teaches the requirement of a six amino acid sequence (described previously). Harris teaches away from for amino acid cleavage site. Boyer teaches the purification of interferon from a fusion protein containing an Xa cleavage site, however the teaching of Xa does not render the current invention obvious. Xa is an entirely distinct protease with different amino acid specificities and requirements for cleavage as discussed above. The addition description of interferon as the protein of interest, does not overcome the deficient teachings. It would not have been obvious to one of skill in the art to combine the teachings of Harris and Boyer to produce an authentic interferon protein by the claimed methods.

Sufficient secondary considerations exist due to the unexpected results associated with claimed method (e.g. Granzyme B efficiencies and cleavage specificities, described under sub-part (A) above.

Claim 8

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Medabalimi, 2000 in view of Harris et al., 1998.

Applicants respectfully submit that the combination of Medabalimi with Harris does not resolve the failure of Johnson, Harris, and Pharmacia to teach or suggest the method of claim 1. Because claim 8 depends from claim 1 (via claim 6), claim 8 includes all the elements of claim 1. Therefore, for the reasons discussed above regarding the patentability of claim 1, Applicants submit that claim 8 is patentable.

The combination of Medabalimi and Harris does not render claim 8 obvious under 35 U.S.C. 103(a). As described repeatedly, Harris does not teach a four amino acid motif for cleavage as cited in the Office Action, but instead teaches the importance of a six amino acid motif. Nor does Harris teach and an authentic protein form. Medabalimi fails to teach a method of making an authentic protein as described in the Office Action. Instead Medabalimi teaches a protease site surrounded both 5' and 3' by lengthy flanking sequences (see Column 6 and Figure 2B). Thus, Medabalimi does teach, suggest, or motivate a method of making an authentic protein from a fusion protein. It would not have been obvious to one of skill in the art to combine the teachings of Harris and Medabalimi to produce Granzyme B or <u>any</u> polypeptide of interest in authentic form.

In addition, sufficient secondary considerations exist due to the unexpected results associated with claimed method (e.g. Granzyme B efficiencies and cleavage specificities, described under sub-part (A) above. Claim 8 is patentable over the combination of Medabalimi and Harris because the combination of art fails to lead one of skill in the art to modify or combine the teachings to arrive at the claimed invention, or (2) because the results of the claimed invention were unexpected.

Claim 16 & 17

Claim 16 & 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Johnson et al., 2000 in view of Harris et al., 1998 in view of Braun et al., 1993.

Applicants respectfully submit that the combination of Johnson and Harris with Braun does not resolve the failure of the combination of Johnson and Harris to teach or suggest the method of claim 1 as discussed above. Because claims 16 and 17 depend

from claim 1, claims 16 and 17 include all the elements of claim 1. Therefore, for the reasons discussed above regarding the patentability of claim 1, Applicants submit that claims 16 and 17 are patentable.

Additionally, the combination of Johnson, Harris and Braun does not render claims 16 and 17 obvious under 35 U.S.C. 103(a). One of skill in the art would not consider conditions ideal for one protease, Xa, to be identical for a distinctly different protease, Granzyme B. Again these enzymes have different amino acids specificities, rates of cleavage, and cleavage efficiencies as described previously. Furthermore a detailed experimental analysis of the optimum concentrations and temperature conditions for Granzyme B-specific cleavage is provided in the specification on page 54 and 55. Braun's passing description of Ni^{2+} and NTA concentrations important for the optimum cleavage of an Xa cleavage site coupled with the deficient teachings of Harris and Johnson (previously discussed) would not render the invention of claims 16 and 17, contacting Granzyme B protease with Ni^{2+} and NTA, obvious to one of skill in the art.

Sufficient secondary considerations exist due to the unexpected results associated with claimed method (e.g. Granzyme B efficiencies and cleavage specificities, described under sub-part (A) above.

In summary, because the six § 103(a) rejections (1) fail to provide combinations of art or teachings that would have led/motivated one of skill in the art to modify or combine the teachings to arrive at the claimed invention, and/or (2) the combinations of art fail to lead one of skill in the art to predict the claimed invention, and (3) the results of the claimed invention were unexpected. The above arguments render the claims patentable over any of the applied references, thus Applicants respectfully request Examiner to withdraw this rejection for claims 1-11 and 13-17.

CONCLUSIONS

Applicants submit that all of the rejections and objections in the Office Action have been addressed with the forgoing arguments and amendments. Applicants do not waive any argument by failing to make the argument here. Applicant expressly reserve the right to reassert the above arguments, or assert additional arguments in the future.

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If the Examiner believes it to be helpful, he is invited to contact the undersigned representative by telephone at 312-913-3344.

Respectfully submitted,

McDonnell Boehnen Hulbert & Berghoff LLP

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